APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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The Examiner further alleges that "[c]ompound II of Miller is structurally very close to that of the compound claimed in instant claim 29 except that the carbonyl group in the base is not present as an enolate. But such an enolate structure is an important intermediate as taught by Fox (above)." (Emphasis added). *See* page 3, ¶4 to page 4, ¶1 of the Office Action.

Applicants assert that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants traverse the rejection for the following reasons:

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) reviewed the analysis for determining if an invention is obvious over the teachings of the prior art and affirmed the factual analysis set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). *KSR*, 127 S. Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18). The factual inquiries necessary in an analysis of obviousness by the Office is delineated in MPEP § 2141 as follows:

> (A) Determining the scope and contents of the prior art;
>
> (B) Ascertaining the differences between the prior art and the claims in issue;
>
> (C) Resolving the level of ordinary skill in the pertinent art; and
>
> (D) Evaluating evidence of secondary considerations ...

MPEP § 2141 further states that:

> When applying 35 U.S.C. 103...
>
> (A) The claimed invention must be considered as a whole;
>
> (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
>
> (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
>
> (D) Reasonable expectation of success is the standard with which obviousness is determined.

Application of the obviousness analysis of KSR, *supra*, was discussed in the recent decision by the Court of Appeals for the Federal Circuit in the chemical case *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (CAFC 2007). The CAFC held that:

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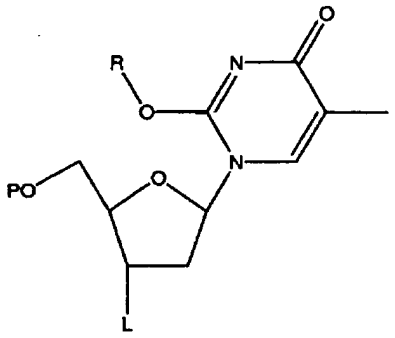
"[w]hile the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person skilled in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis". *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.*"

Applicants' herein would apply the claimed invention consistent with Graham analysis and the ruling in *KSR*, and will show that Applicants' claimed invention meets the criteria of 35 U.S.C. §103.

Claims 1-32 are directed to compounds of the following formula[1]:



Applicants' invention is directed to the synthesis of radiolabeled nucleosides in a lesser number of steps and with good yield. It has been known in the art that the 2-*O* group of thymidine can displace leaving groups anti to the 2-*O* group to produce 2,3'-anhydrothymidine. To prevent the unwanted formation of this 2,3'-anhydrothymidine, the 3-N group on the pyrimidine ring has been alkylated to prevent the participation of nitrogen in tautomer formation and thereby to prevent the attack of 2-*O* group on the leaving group anti to its position. The alkylation of the 3-N group of the pyrimidine, however, takes place in 7 steps and results in a poor yield of ^{18}F-FLT of 20%, after deprotection. *See* page 2, [0006] and [0007] of the application as filed.

Applicants' invention prevents this formation of 2,3'-anhydrothymidine from thymidine derivatives and results in the formation of a precursor of ^{18}F-FLT in only 3 steps and in 85% yield. *See* Example, pages 10-11 of the application as filed. Therefore, Applicants invention unexpectedly provides a short and simple method to prepare radiolabeled nucleosides with a high yield.

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[1] This brief summary is provided for illustrative purposes only and is not to be construed as limiting, modifying or altering the scope of each of the independent claims provided. The Examiner is requested to review the independent claims to determine the exact scope of the claimed invention.

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In order to expedite prosecution, Applicants have amended the method Claims 1-20 to define the reagent that enolates the reaction product of step (a) which is either an alkoxide (Claims 10 and 12) or an alkoxide having 1 to 4 carbons, cycloalkoxide C_3-C_6, phenoxide, tosyate, acetate, or benzoate (Claim 1). Applicants have amended compound Claims 21 and 30 to recite the protecting groups.

Applicants summarize the differences between the cited art and the claimed invention as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), cited in MPEP 2142.

1. Fox et al. in combination with Miller et al. do not teach either the reagents to prepare the product or the product of the claimed invention

A method for preparing a compound requires at least a starting material, a reagent and the resulting compound. Fox et al. do not teach any of these elements of the present application. Fox et al. do not teach 2,3'-anhydrothymidine derivative which is a starting material as claimed in the present application. Fox et al. teach a 2,5'-anhydrothymidine derivative as a starting material to prepare the compound 8.

The Examiner cites Miller et al. to provide 2,3'-anhydrothymidine derivative. Miller et al. however, merely discloses a 2,3'-anhydrothymidine derivative. Miller et al. do not teach or suggest the opening of the 2,3'-anhydrothymidine derivative to form an enolate, instead the 2,3'-anhydrothymidine derivative of Miller et al. opens up back to the thymidine derivative.

Fox et al. do not suggest or motivate a person of ordinary skill in the art to replace the 2,5'-anhydrothymidine derivative with the 2,3'-anhydrothymidine derivative and conduct a ring opening reaction to make the enolate product of the present application.

> "For a chemical compound, a prima facie case of obviousness requires 'structural similarity between claimed and prior art subject matter ... where the prior art gives reason or motivation to make the claimed compositions.'" *In re Dillon,* 919 F.2d 688, 692 (Fed. Cir. 1990) *(en banc).* In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the

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prior art" for the change in the structure. In re Grabiak, 769 F.2d 729, 731-732 [226 USPQ 870] (Fed. Cir. 1985).

"Because of the unpredictable nature of chemical reactions, a newly-synthesized compound may be very similar in structure to known and existing compounds and yet exhibit very different properties. Further, many such new compounds are obvious in the sense that any competent chemist could have synthesized them *if requested or motivated to do so.*" 2 Donald S. Chisum, Chisum on Patents §5.04[6] at 5-429 (2000) (emphasis added).

To show obviousness, the reason or motivation offered by the prior art need not offer "absolute predictability" of the results, but it requires at least a "reasonable expectation of success." *Yamanouchi,* 231 F.3d at 1343, quoting *In re Longi,* 759 F.2d 887, 896 (Fed. Cir. 1985); accord, *In re Vaeck,* 947 F.2d 488, 495 (Fed. Cir. 1991) (reversing PTO rejection of claims as obvious where prior art offered no "reasonable expectation of success"), citing *In re O'Farrell,* 853 F.2d 894, 903-04 (Fed. Cir. 1988). If the prior art makes a particular experiment or modification only "obvious to try," that does not support a finding of obviousness. See *In re Eli Lilly and Co.,* 902 F.2d 943, 945 (Fed. Cir. 1990), citing *In re O'Farrell,* 853 F.2d at 903.

The 2,5'-anhydrothymidine derivative of Fox et al. is a cyclic ring formed between the primary carbon at the 5' position with the 2-O of the pyrimidine ring. This ring formation results in two cyclic rings, one is 7-membered cyclic ring and the other is 8-membered cyclic ring. The 2,3'-anhydrothymidine derivative of the claimed invention is a cyclic ring formed between the secondary carbon at the 3' position with the 2-O of the pyrimidine ring. This ring formation results in two cyclic rings, one which is 6-membered cyclic ring and the other is 7-membered cyclic ring.

It is well known in the art that the stability of the 6-membered ring is different from the stability of the 7- or 8-membered ring. Therefore, the stability of the 2,5'-anhydrothymidine derivative of Fox et al. will be different from the stability of the 2,3'-anhydrothymidine derivative of the claimed invention. In turn, the reactivity of the two derivatives in a certain reaction would also be different.

In the absence of suggestion or motivation in Fox et al. or Miller et al. and because of the unpredictable nature of chemical reactions, a person of ordinary skill in the art will have no reasonable expectation of success in replacing the 2,5'-anhydrothymidine derivative of Fox et al. with the 2,3'-anhydrothymidine derivative to arrive at the claimed invention.

The Examiner alleges that, "[e]ven though the structure of the anhydro derivatives are slightly different in both Fox and Miller one of ordinary skill in the art will recognize that the same sequence of steps can be applied to make the compound in instant claim 1 via the steps as instantly claimed with slight modifications." *See* page 4, ¶1 of the claimed invention. (Emphasis added).

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Applicants respectfully disagree. As pointed out above, the structure of 2,5'-anhydrothymidine derivative is not slightly different from the structure of 2,3'-anhydrothymidine derivative. This difference in the structure relates directly to the relative stability and the reactivity of the two derivatives. A person of skill in the art will have no reasonable expectation of success in replacing the 2,5'-anhydrothymidine derivative of Fox et al. with the 2,3'-anhydrothymidine derivative to arrive at the claimed invention.

Further, neither Fox et al. nor Miller et al. disclose the reagents used in the claimed invention to result in the enolate product of the claimed invention. Miller et al. teaches refluxing with alkali to open the ring of 2,3'-anhydrothymidine derivative back to the thymidine derivative (*see* Miller et al. page 936, right hand column, ¶1). Fox et al. teach preparation of compound 8 from compound 4 using hot methanol with triethylamine (*see* Fox et al. page 1593, right hand column, ¶1). Fox et al. do not teach preparation of compound 8 from compound 4 using an alkoxide having 1 to 4 carbons, cycloalkoxide C_3-C_6, phenoxide, tosyate, acetate or benzoate, as in the present application.

Indeed, the conversion of compound 4 to compound 8 may not be feasible in alkoxide or the other reagents of the claimed invention as the mesylate at the 3' position, which is a good leaving group, may also get cleaved in the presence of these reagents. In contrast, the reagent used for the formation of enolate, an alkoxide having 1 to 4 carbons, cycloalkoxide C_3-C_6, phenoxide, tosyate, acetate, or benzoate, as in the claimed invention, does not cleave the protecting group at the 5' position.

There is no suggestion nor motivation in either Fox et al. or Miller et al. to replace the 2,5'-anhydrothymidine derivative of Fox et al. with the 2,3'-anhydrothymidine derivative and further to replace the reagent of Fox et al. with the reagent of the claimed invention and arrive at the product of the claimed invention. A person of ordinary skill in the art will have no reasonable expectation of success in replacing both the starting material and the reagent of Fox et al. to arrive at the claimed invention.

Furthermore, neither Fox et al. nor Miller et al. disclose the enolate product of the claimed invention. Miller et al. does not disclose the enolate product of the claimed invention. The compound 8 of Fox et al. does not have a protected 5' position. The presently amended Claims 21-22 and 25-31 recite specific protecting groups, none of which are disclosed in Fox et al. There is no suggestion or motivation in Fox et al. or Miller et al. to protect the 5' position of compound 8 and arrive at the claimed product.

The Examiner alleges that, "[i]t is well within the purview of one of ordinary skill in the art to substitute other protecting groups and leaving groups as instantly claimed since all of these groups are well known in the art ...." *See* page 4, ¶3 of the Office Action.

Applicants point out to the Examiner that the protection of the 5' position in the claimed invention is not after the formation of the enolate product. Instead the 5' position is protected before the ring opening reaction of 2,3'-anhydrothymidine to prevent the reaction at the 5' position. In contrast, the 5' position does not need to be protected in Fox et al. since the 5' position is forming a cyclic ring to form 2,5'-anhydrothymidine derivative. There is no suggestion or motivation in Fox et al. to

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manipulate this protection of the 5' position to arrive at the claimed product. Applicants assert that the Office has resorted to impermissible hindsight.

> The requirement "at the time the invention was made" is to avoid impermissible hindsight. "It is difficult but necessary that the decision maker forget what he or she has been taught . . . about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the **art. >...<" *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

The Office has cited two different arts to combine the elements of the claimed invention where none of the cited art individually or in combination teach, suggest or motivate a person of ordinary skill in the art with any reasonable expectation of success to arrive at the claimed invention.

Fox et al. do not teach nor suggest the method, the purpose nor the motivation for adding a hydroxyl protecting group to the 5' hydroxyl group of compound 8 to form the compound as recited in claimed invention, as such an extra step in the process are not useful, feasible nor efficient.

Applicants submit that in the absence of any suggestion or motivation in Fox et al. and Miller et al., a person of ordinary skill in the art will have no reasonable expectation of success in replacing the starting material, the reagent, and the product of Fox et al. to arrive at the claimed invention.

2. Fox et al. teaches away from the claimed invention

Applicants reiterate[2] that Fox et al. teaches away from the claimed invention.

> A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

The bicyclic compound 8 taught by Fox et al. is an intermediate containing a 5' hydroxyl derivative of thymidine that was prepared by the hydrolysis of compound 4. *See* figure 2, page 1593. In addition, as an intermediate that is useful for the preparation of other biological active compounds, such as compound 6 as noted by the Examiner, Fox et al. teach that according to the reaction process, compound 8 must be formed as the free 5' hydroxyl derivative of thymidine under the hydrolysis condition such that the process for the reaction of compound 8 with liquid ammonia forms the desired compound 6. Fox et al. further teach that various derivatives of the tricylic compound 6 may then be prepared from compound 8.

Accordingly, Fox et al. teach that the preparation of compounds of biological interest such as compound 6 may be prepared by using intermediate compounds such as

[2] Response filed Sept. 17. 2007, page 10

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8, and the intermediate compound 8 with the 5' unprotected hydroxyl derivative are prepared and further employed to synthesize the tricyclic compound 6.

Accordingly, one skilled in the art examining the disclosure of Fox et al. would have been motivated to simply use the free 5' hydroxyl compound 8 to prepare various biologically active compounds such as the tricyclic compound 6, and would not have been motivated to prepare a derivative of compound 8 to form the 5' hydroxyl protected compounds recited in Claim 21 and Claim 30. That is, the intermediate compounds taught by Fox et al. are different, the process is different and the resulting products formed form this process is different from the compounds recited in Claim 21 and Claim 30.

3. Unpredictability in the art

Supreme Court in *KSR* noted that exemplary rationales that may support a conclusion of obviousness include:

> (A) Combining prior art elements according to known methods to yield predictable results;
>
> (B) Simple substitution of one known element for another to obtain predictable results;
>
> (C) Use of known technique to improve similar devices (methods, or products) in the same way;
>
> (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
>
> (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
>
> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

It is well known that the field of chemical reactions is not a predictable field. As is shown *supra*, 2,5'-anhydrothymidine derivative and the 2,3'-anhydrothymidine derivative will differ in their stability and reactivity. In the absence of any teaching, suggestion or motivation in any of the cited references, a person of ordinary skill in the art will have no reasonable expectation of success to replace 2,5'-anhydrothymidine derivative with 2,5'-anhydrothymidine derivative and use a different reagent for the enolation reaction to arrive at the claimed invention.

Applicants reiterate that in contrast to the Examiner's statement that "Fox teaches the conversion of the anhydro intermediate 4 to the derivative 5, which is the same as the compound obtained in step (c) of the present Claim 1," the conversion of intermediate 4 to derivative 5 (Figure 2, page 1593) is not the same nor even similar to the compound of

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step (c) in Claim 1 of the present application, for the following important reasons. First, compound 4 of Fox is a tricyclic derivative, while the compounds in step (b) and step (c) are bicyclic derivatives.

Second, Fox et al. teach the use of a tricyclic ether derivative 4 (i.e., oxygen contain compound) as the starting material, but the reaction forms the intermediate compound 5 that is a nitrogen containing compound (by replacement of the oxygen with nitrogen using ammonia). Applicants note that in Claim 1 of the present application, no such conversion of an oxygen atom to a nitrogen atom is claimed; nor does step (b) or step (c) in Claim 1 of the present application forms a tricyclic compound as taught by Fox et al.

The Examiner also rejected the trityl enolate compound recited in Claim 29, citing Miller et al. who disclose a thymidine derivative II (page 936, Figure 1) as being "structurally very close" to the compound claimed in Claim 29, "except that the carbonyl group in the base is not present as an enolate," and the Examiner comments that "such an enolate structure is an important intermediate taught by Fox (above)." The Examiner further note that

> "Fox teaches the conversion of the anhydro intermediate 4 to the derivative 5, which is the same as the compound obtained in step (c) of instant claim 1. A derivative that structurally similar to the compound in step (a) of claim 1 (the protected derivative) is taught by Miller (structure III of Miller in Figure 1). Even though the structure of the anhydro derivatives are slightly different in both Fox and Miller one of ordinary skill in the art will recognize that the sequence of steps can be applied to make the compound in instant claim 1 via the steps as instantly claimed with slight modifications. Such a modification based on the prior art is well within the purview of one of ordinary skill in the art.
>
> Based on the teachings of the prior art, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make compounds as claimed in instant claims 21-30 via the process as claimed in instant claims 1-20 since structurally very close compounds as instantly claimed and steps for the same are seen to be taught in the prior art." (Emphasis added)

Applicants respectfully traverse the Examiner's characterization of the cited art references as applied to Applicant's invention.

As noted above, because of the unpredictable nature of the chemical reactions and the resulting compounds and intermediates prepared from these reactions is particularly pronounced, the Examiner's observation that the thymidine derivative II (page 936, Figure 1) as being "structurally similar," or "structurally very close" to the compound claimed in Claim 29; and that the structure of Claim 1 in the present application is "slightly different" are not the appropriate standards for establishing a *prima facie* case of obviousness. In addition, the Examiner cited the process of Fox et al. for the conversion of compound 4 to compound 5, suggesting that the process is "the same as the compound obtained in step (c) of instant claim 1." However, as detailed above, the process taught by Fox et al. is significantly distinct from the process of Claim 1 of the present application, because the intermediates are different, the process step and

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reagents used are different, and the resulting products taught by Fox et al. is also different than those recited in Claim 1 of the present application.

Finally, in addition to the different compounds taught by Fox et al. and by Miller et al., neither Fox et al. nor Miller et al. teach nor suggest the process recited in Claim 1 of the present application.

For the reasons as provided above, Applicants respectfully request the withdrawal of the 35 U.S.C. 103(a) rejection of Claim 1-32.

Applicants respectfully assert that Claims 1-32 are novel, and allowance of these claims is respectfully solicited. The present application is believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

In view of the foregoing amendments and remarks, Applicant submits that all of the claims are in proper format and are patentably distinct from the prior art of record and are in condition for allowance.

The Examiner is invited to contact the undersigned at the telephone number listed below with and questions concerning this application.

Respectfully submitted,

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SVCA_196114.1